



Role of Intrathecal Hydrocortisone and Hyaluronidase in Tubercular Meningitis

Authors

**Dr Tejpal Singh^{1*}, Dr Sangita Aneja², Dr Rupali Malhotra³, Dr Balbir Singh⁴
Dr Kushal Pal⁵**

¹Professor, Dept. of Medicine, ²Professor and Head Dept of Radiology, LLRM Medical College, Meerut
³J.R., Dept. of Medicine, ⁴Professor, Dept. of Medicine, ⁵J.R Dept of Medicine

Corresponding Author

Dr Tejpal Singh

Professor, Dept. of Medicine, S.N. Medical College, Agra, UP, India

Abstract

Aim and Objective: To assess the effectiveness of intrathecal hydrocortisone, hyaluronidase and intravenous magnesium sulphate in cases of tuberculous meningitis.

Methods: The present study was carried out in the Postgraduate Department of Medicine, S.N. Medical College, Agra, comprising of 60 cases to tubercular meningitis. The diagnosis was suspected on clinical ground and confirmed by cerebrospinal fluid examination and associated CT scan findings. The patients were divided into 3 groups. 20 patients of Group A received treatment with antitubercular drugs and systemic steroids in standard dosages. 20 patients of Group B received intrathecal hyaluronidase (1500 IU) + intrathecal hydrocortisone (50 mg) in addition. 20 patients in Group C received intravenous magnesium sulphate in addition to standard treatment.

Result: The result were analyzed at 3 weeks and 6 weeks. Regular follow up examination was done at 1 – 2 month interval. Final results were analyzed according to the latest follow up report available. The basis of analyzing the result was the improvement in the clinical outcome of the patients along with change in cerebrospinal fluid. There was reduction in cerebrospinal protein in all 3 group but reduction in cerebrospinal fluid protein was more in Group B receiving intrathecal therapy as compared to other Groups and this was statistically significant. Clinical evaluation of patients was done on day 1, 7, 42 in different groups using modified rankin score and Barthel index. It was found that recovery was much faster and clinical improvement occur earlier in patients receiving intrathecal therapy. Magnesium sulphate although did not caused rapid resolution of cerebrospinal fluid but it helped in earlier clinical improvement in patients especially those with tubercular arteritis.

Conclusions: Intrathecal hyaluronidase and hydrocortisone as an adjuvant to antitubercular treatment is very useful in cases of tuberculous meningitis particularly at advanced stage of disease, Magnesium sulphate when given intravenous to patients of tubercular meningitis with arteritis helps in early clinical recovery as evidenced by change in Barthel Index and Modified Rankin Index.

Introduction

Tuberculosis is one of the most important chronic infection worldwide. Presently, more than 2

billion people in the world are infected with tuberculosis (i.e., one third of the world's population), of which approximately 10% will

develop clinical disease. The incidence of central nervous tuberculosis is related to the prevalence of tuberculosis in the community, and it is still the most common type of chronic central nervous system infection in developing countries (Tarachand Ramachandra et al¹ 2008).

Tuberculosis of central nervous system constitutes about 5% of extra pulmonary tuberculosis and associated with high mortality and morbidity. Three clinicopathological categories of central nervous system tuberculosis are meningitis, tuberculoma (intracranial and spinal), arachnoiditis (basal, optochiasmatic, spinal). Tubercular meningitis constitutes about 80% of central nervous system tuberculosis (Gautam Ahluwalia et al 2005²). Tubercular meningitis occurs due to infection with mycobacterium tuberculosis. The air borne M. tuberculosis reach alveoli where they multiply and disseminate through blood stream to lodge in different organ including meninges.

Tubercular meningitis requires early detection and institution of appropriate chemotherapy as it can potentially lead to 100% recovery without sequela (Fitz Simon 1963³). Untreated disease is fatal within 3 to 8 weeks of presentation and carries a high risk of neurological sequelae. If therapy is delayed (Molavi et al⁴ and Lefock 1985, Ogawa et al⁵).

As in other forms of tubercular meningitis successful chemotherapy requires the use of multiple drugs to which organism is sensitive. However treatment of central nervous system tuberculosis has two challenges. The identification of drug that reliably penetrate cerebrospinal fluid and brain parenchyma and the ongoing search for measures that curtail brain damage from residual disease and from the healing process itself.

Currently following antitubercular drugs penetrate CSF INH (100%), PZA (100%), ethionamide (100%), cycloserine (80 – 100%), rifampicin (10 – 20%), ethambutol (100%) in inflamed meninges, PAS (10 – 15%), streptomycin (20%) in inflamed meninges, linezolid (20%).

Despite the treatment with antitubercular drugs in appropriate combinations and doses, complication of tubercular meningitis may occur. This is particularly true for advanced stage of disease. Clinical picture and complications of TBM are due to thick basilar exudates, vasculitis, allergic reaction tuberculoprotein and cerebral edema. As penetration of antitubercular drugs are already poor in meninges these factors especially exudates may contribute to inadequate drug concentration at disease site and thus recovery may be delayed and complications may set in despite appropriate antitubercular treatment. So there is need for some adjunct therapy, so that recovery can be accelerated and complications can be prevented/reduced by ensuring adequate drug concentration as lesion sites.

The response of steroid may be dramatic with rapid clearing of sensorium, regression of abnormalities in cerebrospinal fluid, defervescence and relief of headache. Trials suggest that these agents may be beneficial in patients with significantly elevated intracranial pressure to prevent brain herniation and in those with impending spinal block with high cerebrospinal fluid protein levels.

The enzyme hyaluronidase reduces the viscosity by hydrolyzing the glucosaminidic bonds of hyaluronic acid and other mucopolysaccharides of the ground substance, leading to enhancement of absorption of exudates, resolution of adhesions and facilitating diffusion of drugs. The enzyme has being found to be nontoxic to man on subcutaneous or intravenous administration. Even administration in pleural, peritoneal or subarachnoid spaces is virtually free of any side effect. These properties of hyaluronidase associated with its safety lead to its use in intrathecal route in treatment of tubercular meningitis as an adjunct to antitubercular drugs.

Magnesium sulphate is being used in various medical condition and may be beneficial in many disorder like asthma, cardiac arrhythmia, eclampsia, headache, hypertension, mania, mitral valve prolapsed, muscle cramp, seizure, tetanus

and vasospastic disorder. Some studies document the role of magnesium sulphate in ischemic stroke. It by its neuroprotective role helps in early recovery from stroke. In our study we are going to evaluate role of magnesium sulphate in tubercular meningitis especially those with tubercular arteritis.

Methods

Approximately 60 patients of tubercular meningitis were selected from Department of Medicine and paediatrics S.N. Medical College and Hospital Agra. After taking informed consent for study each case of tubercular meningitis was subjected to detailed clinical history from patient and their attendants. For the presenting illness, history of fever, headache, vomiting, convulsions, paralysis, altered sensorium and unconsciousness was taken. History was also taken for any simultaneous cough, chest pain and hemoptysis to look after any coexisting pulmonary lesion. Symptoms of loss of appetite, loss of weight, cachexia and night sweats were reviewed. In the past illness, history of tuberculosis, BCG – vaccination, diabetes mellitus and meningitis will be taken along with history of treatment prior to hospitalization. A thorough general examination and detailed neurological assessment will be made in addition to systyemic examination.

Each patient was subjected to the following laboratory investigations. Hematological profile i.e. Hemoglobin, Total and Differential counts and ESR. Urine analysis for albumin, sugar and microscopic examination. Blood sugar both fasting and two hours after the standard glucose load. Sputum examination for the presence of acid fast bacilli using Ziehl Neelson staining technique. X-ray chest P/A view to demonstrate any simultaneous pulmonary Koch's lesion. Lumbar puncture would be done with due precautions and cerebrospinal fluid will be examined as follows –

- a) Microscopic examination e.g. Gross appearance, colour, any deposition and pressure estimation.

- b) Cytological examination for total and differential cell counts.
- c) Examination for AFB in smear and culture for AFB.
- d) Gram staining examination and culture.
- e) Biochemical examination for protein, sugar and chlorides.
- f) DNA analysis by polymerase chain reaction (PCR).

CT scan will be done whenever possible and will be examined for following changes

- ❖ Presence of exudates especially in basal subarachnoid cisterns, sylvian fissures and cistern pontis.
- ❖ Hydrocephalus induced ventricular enlargement.
- ❖ Periventricular leucencies suggesting the presence of ependymal tubercular exudates.

A positive diagnosis for definite TBM was made in cases where CSF smear or, culture will be positive for AFB or PCR positive for AFB. In the absence of above criteria the diagnosis of most probable TBM will be based on Clinical features (History and examination) suggestive of meningitis. Examination of cerebrospinal fluid suggestive of predominantly lymphocytic cells, Rise in the protein level and low CSF sugar level. CT finding suggestive of Exudates, Hydrocephalus and Tissue infarction (feature of atereitis).

All the positively diagnosed cases of TBM will be started standard therapy with antitubercular drugs along with steroids in standard doses.

Unmarked sealed envelope containing directives for group A, B and C were prepared in advance and drawn at random. Patients were thus assigned to 1 to 3 therapeutic regimens.

Group A – Standard therapy only.

Group B – Standard therapy plus intrathecal hyaluronidase (1500 IU) and hydrocortisone hemisuccinate (50mg).

Group C - Standard therapy plus intravenous magnesium sulphate (2 gm overy 6 Hourly).

Duration

Intrathecal therapy was given biweekly initially for 2 – 3 weeks and thereafter weekly observing strict aseptic precaution. Total duration of therapy was be 4 – 6 weeks. Patients in stage I will be given intrathecal therapy for 1 week. Intravenous magnesium sulphate was be given for 7 days.

Dosage

In group B hyaluronidase and hydrocortisone diluted in 2 ml of sterile water to ensure adequate distribution in cerebrospinal fluid. Prior to giving intrathecal hyaluronidase a sensitivity test will be done.

In group C 2gms of magnesium sulphate in dilution with 100 ml normal saline was given every 6 hrs for 7 days.

Assessment

A CT scan was performed before starting treatment. Cerebrospinal fluid examination was

done every time whenever lumbar puncture carried out for intrathecal therapy in group B. In the control group (Group A) and Group C receiving antitubercular treatment lumbar puncture was done at 3 week and 6 week interval to compare the result with other groups. Serum and CSF magnesium levels was done at start of therapy and at 7 day of therapy in all 3 groups. A repeat CT Scan was done after 3 months of therapy in patients who could be able to afford it.

All patients were followed up for a minimum period of 6 weeks and often longer whenever possible after discharge. A clinical assessment of the neurological state of the all patients will be made at day 1, 7 and 42. The following scales are used for evaluation at day 1, 7 and 42 days.

Barthel index (BI).

Modifies Renkin Scale (MRS).

Barthel Index:

	<u>With Help</u>	<u>Independent</u>
1. Feeding (if food needs to be cut up help)	5	10
2. Moving from wheel chare to bed & return (includes sitting up in bed)	5 – 10	15
3. Personal toilet (wash face, comb, hair, Shave clean, teeth)	0	15
4. Getting on & off toilet (handling clothes, Wipe, flush)	5	10
5. Bathing self	0	5
6. Walking on level surface (or if unable to walk, propel wheel chair) Score only if unable to walk	0	5
7. Ascend & descend stairs	5	10
8. Dressing (includes tying shoes)	5	10
9. Controlling bowels	5	10
10. Controlling bladder	5	10

Modified Rankin Scale

<u>Score</u>	<u>Description</u>
0	No symptoms at all.
1	No significant disability despite symptoms; able to carry out all usual duties and activities.
2	Slight disability; unable to carry out all pervious activities, but able to look after own affairs without assistance.
3	Moderate disability; requiring some help, but able to walk without assistance.
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention.
6	Dead.

Observations

60 cases admitted in the P. G. Department of Medicine and Paediatrics, S. N. Medical College, Agra constituted the material for present study. All the patients included under the study were randomly allotted to one of the three study group. Out of 60 patients included in the study 20 (33.33%) received standard treatment with

antitubercular drugs and systemic steroid only and thus served as control group (A). 20 (33.33%) patients in group B in addition to standard treatment received intrathecal hydrocortisone (50 IU) and hyaluronidase (1500 IU). 20 patients in group C in addition to standard therapy received intravenous magnesium sulphate.

Table -1 Number of Cases and Different Groups

S.No.	Treatment	Group	Cases	
			No.	%
1	Standard treatment only	A	20	33.33
2.	Standard treatment + Intra-thecal hyaluronidase and hydrocortisone	B	20	33.33
3.	Standard treatment + Magnesium sulphate	C	20	33.33

Table -2 Age and Sex Distribution in Different Groups

Age (Years)	Group A			Group B			Group C			Total		
	M	F	T	M	F	T	M	F	M	F	T	
	12	8	20	11	9	20	12	8	20	35	25	60

As is clear from Table -2, the cases are distributed into all age groups. Although cases are distributed in all age groups, maximum number of cases were in the second and third decade of life. When compared in different treatment groups, the

number of cases in male compared to female ratio was 1.4 : 1.

All patients in 3 groups were assessed clinically on day 1, day 7 and day 42 and given disability index score Modified Rankin score (MRS) and Barthel index (BI).

Table – 3 Comparison of Change of Modified Rankin Score in Study Group with Control

		Group A – B	Group A – C
Day 1 – 7	p value	0.032	0.17
	t value	2.12	1.4
Day 1 – 42	p value	0.032	0.18
	t value	2.23	1.37

It was found that mean of modified rankin score change in Group A from day 1 to day 7 and day 1 to day 42 was 0.89 ± 0.59 and 1.5 ± 0.69 respectively and in Group B was 1.25 ± 0.59 and 2 ± 0.73 while comparing the results of Group A and B in table 3 it was found that this difference was statistically different $p = 0.0$; ($p < 0.05$); Though there was more change of modified rankin score in Group C as compared to Group A, mean fall from day 1 – 7 are 1.17 ± 0.55 and day 1 – 42 are 1.80 ± 0.70 and this as compared to Group A but it was not statistically significant.

Table 4 compares changes in patients of Group A and C who were having arteritis. When patients having arteritis were considered it was found that change of modified rankin score in Group C was more as compared to Group A and it was statistically significant.

Table – 4 Comparing Modified Rankin Score of Patient Having Arteritis

Days	Group A		Group C		p value (A – C)
	Mean	SD	Mean	SD	
1 – 7	0.80	0.45	1.43	0.53	0.05
1 – 42	1.2	0.45	2.14	0.69	0.03

Table – 5 Comparison of Barthel Index of Study Group with Control

		Group A – B	Group A – C
Day 1 – 7	p value	0.049	0.17
	t value	2.03	1.3
Day 1 – 42	p value	0.045	0.18
	t value	2.07	1.4

It was found that mean of barthel index change in Group A from day 1 to day 7 and day 1 – 42 was 11 ± 15.44 and 17.25 ± 22.03 respectively and in Group B was 21 ± 17.9 and 32 ± 23.73 , while comparing the result of Group A and B in table 5 it was found that this difference was statistically significant $p = 0.045$; ($p < 0.05$).

Though there was more change in barthel index in Group C as compared to Group A, mean of change from day 1 – 7 are 13 ± 13.22 and day 1 – 42 are 32 ± 25.31 but it was not statistically significant.

When patients having arteritis were considered it was found that change of Barthel index in Group C was more as compared to Group A and it was statistically significant.

Table 6 shows the comparison of the CSF analysis between different groups at the time of presentation and at final evaluation. In group A the mean protein level decrease from 184 to 117. In group B CSF protein was decreased from 196 to 96.2 and in group C the protein level decreased from 172 to 101.

Table – 6 Comparison of CSF Analysis between Different Groups before Treatment and At 3 Wks and 6 Wks

Content (Mean ± SD)	Group A			Group B			Group C		
	BT	3 Wks	6 Wks	BT	3 Wks	6 Wks	BT	3 Wks	6 Wks
Protein	184	150.8	117	196	143	96.2	172	142.9	101
	± 80.6	± 59.54	± 40.5	± 90.4	± 57.09	± 18.2	± 80.2	± 57	± 25
Sugar	32.1	49.25	66.2	32.4	48.15	62.1	33.5	50	67.5
	± 6.90	± 5.07	± 6.80	± 10.9	± 10.37	± 8.08	± 6.99	± 7.38	± 8
Total Cell Count	153	106.85	60.3	199	109.75	49.1	173	119.7	57.4
	± 60.6	± 39.60	± 22.1	± 99.1	± 34.1	± 15.6	± 75.6	± 39.23	± 18.7

When comparing changes in CSF of Group B and Group C with Group A in table 7 it was found that fall of protein in group B (107.10) was statistically significant as compared to group A ($p = 0.047$; $p < 0.05$) while fall of protein in group C (73.55) was

not statistically significant as compared to Group A (65.85) ($p = 0.6475$; $p > 0.05$). Comparing the difference between the change in sugar and cell it was not statistically significant.

Table 7 Comparison of CSF Analysis between Different Groups before Treatment and At 3 Wks And 6 Wks

		Group A – B		Group A – C	
		3 Wks	6 Wks	3 Wks	6 Wks
Protein	p value	0.05	0.0473	0.72	0.6475
	t value	1.98	2.0505	0.33	0.46
Sugar	p value	0.09	0.0861	0.57	0.7805
	t value	1.7	1.702	0.56	1.60
Cell	p value	0.093	0.0698	0.275	0.22
	t value	1.6	1.865	1.107	1.22

Discussion

60 Cases admitted in the P. G. Department of Medicine and Paediatrics, S.N. Medical College, Agra constituted the material for present study.

Tubercular meningitis still ranks as an important cause of mortality and morbidity in our country. Despite of the availability of very good first and second line antituberular drugs, the results of treatment in tubercular meningitis, contrary to pulmonary tuberculosis, is still far from satisfactory. The probable causes are endarteritis, exudates induced neurological damage and development of hydrocephalus. These complications were probably related to advanced stage of presentation and inadequate penetration of antituberular drugs at disease site.

The enzyme hyaluronidase by virtue of its action of hydrolyzing the glucosaminidic bonds of hyaluronic acid and other mucopolysaccharides of the ground substance, offers a promising mode of treatment. The intrathecal therapy with hyaluronidase in cases of spinal arachnoiditis as a complication of tubercular meningitis had been used in different studies conducted by Gourie Devi and Satish Chandra Department of Neurology NIMHANS Bangalore, with significantly beneficial results. The intrathecal therapy with hydrocortisone has been carried out in tubercular meningitis by various workers with conflicting results. Controversy still exists about the value of intrathecal therapy in tubercular meningitis. Although some authorities recommend the use of intrathecal therapy, others have abandoned this form of treatment.

A total of 60 proven cases of tubercular meningitis were included in the present study. All the patients were randomly divided into 3 study groups. Patients in group A were given standard antituberular chemotherapy along with oral and parenteral corticosteroids and supportive therapy. Patients in group B in addition to standard treatment received intrathecal hyaluronidase and hydrocortisone group C in addition to standard therapy received intravenous magnesium sulphate.

Although cases were distributed in all age groups, the maximum number of cases were from second to fourth decade. Even in different study groups (i.e. A, B and C), the maximum number of cases were in 3rd decade followed by second or fourth decade of life. This age preponderance might be due to more attention being paid to patients of younger age groups.

There was a male preponderance in all the study groups. Overall male to female ratio was found to be 1.4 : 1. This male preponderance might be due to more attention being towards the male members of family.

Fever and headache was the most consistent symptom in all treatment groups, followed by vomiting. 21 patients (35%) were either altered or unconscious at the time of presentation. Most common sign elicited was neck rigidity (89.64%) followed by Kernig's sign (81.3%). Symptoms and signs were more or less equally distributed in all treatment groups. Thus groups were comparable as regards to clinical presentation.

When patients were accessed clinically on day 1, 7 and 42 it was found that in group A mean change in Barthel Index and Modified Rankin Index was 17.25 ± 22.03 and 1.5 ± 0.69 respectively at end of 42 days while in group B mean change in Barthel Index and Modified Rankin Index was 32 ± 23.02 and 2 ± 0.73 respectively at the end of 42 days. There was statistically significant difference when comparing the clinical improvement between two groups ($p < 0.05$).

While comparing the patients with arthritis in group A and Group C. The mean change in Barthel Index and Modified Rankin Index was 20 ± 7.91 and 1.2 ± 0.45 in group A and 30 ± 5 and 2.14 ± 0.69 in group C. The difference between group A and group C was statistically significant in patients with arthritis. However, when comparing clinical improvement in patients without arthritis of group A and C no statistical difference was found in result of two.

In group A cerebrospinal fluid protein level decreased from mean value of 184 to 117 mg%. Thus the mean of fall was 65.85 ± 44 .

In group B the cerebrospinal protein value decreased from initial, mean value of 196 ± 94.7 to 96.2 ± 18.2 . Thus final the fall in protein level was 107.10 ± 78.25 . This fall as compared to fall in group A was statistically significant $p = 0.043$ ($p < 0.05$).

The initial value of cerebrospinal fluid protein in group C was 172 ± 80.2 . The value decreased after treatment of 101 ± 25 . Thus value mean fall in the protein level was 73.55 ± 60.09 . This fall as compared to fall in group A was not statistically not significant $p = 0.647$.

It is obvious that there is statistically significant decline in protein level in the patients receiving combination of hyaluronidase and hydrocortisone. In the study conducted by Gourie Devi and Satish Chandra⁷ (1991) in cases of spinal arachnoiditis complicating tuberculous meningitis, there was a marked fivefold decrease in mean cerebrospinal protein in patients receiving intrathecal hyaluronidase while in control group there was no significant change. In another study conducted by same workers⁸ (1980) in 14 cases of tuberculous spinal arachnoiditis, there was significant fall in CSF protein levels. In the study conducted by Freiman and Geefhuysen (1970) more fall in CSF protein level was noticed after intrathecal therapy with hydrocortisone as compared to control group, but it was not statistically significant. A study was conducted by Bhagwati and George¹¹ (1986) to evaluate role of intrathecal hyaluronidase in management of tubercular meningitis with hydrocephalus in comparison to shunt surgery. The study shows that intrathecal hyaluronidase does in most cases, lead to improvement in the sensorium but does not offer any particular advantage over shunt insertion in terms of regression of specific neurological deficit or overall functional improvement. Thus, observations in the present study coincides with the studies of past.

The rise in cerebrospinal fluid sugar level was observed in all groups. Mean rise in cerebrospinal

fluid sugar level was 34.60, 30.70, 34.05 and A, B and C respectively. These changes were not statistically significant. No relationship could be drawn between the level of CSF sugar at presentation and final outcome. Total cell count decreased in all groups. The mean decrease in total cell count was 114.60, 119.60 and 93.15 in group A, B and C respectively. The fall in cells count among different group was not statistically significant in any group. No significant difference was found among different group in cerebrospinal fluid cells count.

In the study conducted by Freiman and Geefhuysen⁶ (1970) survival and good to fair results were more in patients who received intrathecal therapy with hydrocortisone and streptomycin as compared to control group. A good to fair result was obtained in 50% of survivor in control group while it was 62% in intrathecally treated group. Fall in the mortality was observed in intrathecally treated group by 15%.

In a study conducted by M Sadeh¹⁰ supports the concept that cerebral vasospasm is involved in the pathogenesis of eclampsia. Magnesium which has a beneficial effect eclampsia, may act by opposing calcium dependent arterial constriction, thereby relieving vasospasm. Magnesium may also antagonize the increase in intracellular calcium concentration caused by ischemic and thus prevent cell damage and death. Magnesium might have a role in the treatment of cerebral vasospasm and ischemic such as occurs in subarachnoid hemorrhage, ischemic stroke and brain trauma. Muir et al⁹ (2002) found that systemically administered magnesium at doses that double physiological serum concentration significantly reduces infarct volume in animal models of stroke with a window of upto six hours after onset and favorable dose response characteristics when compared with previously tested neuroprotective agents.

Conclusion

Intrathecal hyaluronidase and hydrocortisone as an adjuvant to antitubercular treatment is very useful in cases of tuberculous meningitis particularly at advanced stage of disease. It decreases the incidence of various complications and increases the rapidity of recovery. By causing the precipitous fall in cerebrospinal fluid protein level and rapid resorption of exudates, it is helpful in preventing spinal block. It may be useful in cases of communicating hydrocephalus.

Intrathecal therapy with hyaluronidase and hydrocortisone can be recommended at advanced stage of tubercular meningitis to prevent various complications and to enhance recovery.

Magnesium sulphate when given intravenous to patients of tubercular meningitis with arteritis helps in early of clinical recovery as evidenced by change in Barthel Index and Modified Rankin Index.

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